Comparison of Mental Stress–Induced Myocardial Ischemia in Coronary Artery Disease Patients With Versus Without Left Ventricular Dysfunction*

Ola Akinboboye, MD, David S. Krantz, PhD, Willem J. Kop, PhD, Sari D. Schwartz, BA, Joseph Levine, MD, Albert Del Negro, MD, Pamela Karasik, MD, Daniel S. Berman, MD, Mark O'Callahan, BS, Karen Ngai, BS, and John S. Gottdiener, MD

To examine the susceptibility to myocardial ischemia with mental stress in patients who have coronary artery disease and normal left ventricular (LV) function versus those who have impaired LV function, we examined 58 patients who had coronary artery disease, including 22 who had normal LV function (ejection fraction ≥50%), 16 who had mild to moderate LV dysfunction (ejection fraction 30% to 50%), and 20 who had severe LV dysfunction (ejection fraction ≤30%) and underwent bicycle and mental stress testing with myocardial perfusion scintigraphy on consecutive days in random order. Ischemia was assessed based on summed difference scores in regional rest versus stress myocardial perfusion and defined as a summed difference score >3. At comparable double products across the 3 groups, ischemia was induced with mental stress more frequently in patients who had severe LV dysfunction (50%) than in those who had normal LV function (9%; p <0.01). The frequency of exercise-induced ischemia was different only between those who had mild/moderate LV dysfunction and those who had normal LV function (56% vs 18%, respectively, p <0.05). The pattern of mental stress versus exercise ischemia differed between groups (p <0.02): there was a higher prevalence of mental stress ischemia versus exercise ischemia in patients who had severe LV dysfunction (p = 0.06), a marginally higher prevalence of exercise versus mental stress ischemia in those who had moderate LV dysfunction (p = 0.07), and no difference in mental stress versus exercise ischemia in those who had normal LV function. Thus, at comparable double products during mental stress and similar extent of coronary artery disease, ischemia with mental stress was induced more frequently in patients who had severe LV dysfunction than in those who had normal LV function. These data suggest that mental stress ischemia may be of particular clinical importance in patients who have coronary artery disease and LV dysfunction. ©2005 by Excerpta Medica Inc.

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Left ventricular (LV) dysfunction has been established as an important predictor of poor outcome in coronary artery disease (CAD).[1,2] However, because of technical limitations in the assessment of ischemia using LV systolic indexes in patients who have severely impaired LV function, previous studies of mental stress ischemia have included only patients who had CAD and normal LV function or mild/moderate LV dysfunction.[3–15] It is not known whether mental stress ischemia can be induced in patients who have severe LV function or if susceptibility to ischemia with mental stress differs between patients who have CAD and normal LV function versus severely impaired LV function. This study compared the frequency of ischemia with mental stress and exercise between patients who had CAD and severe LV dysfunction and those who had CAD and mild to moderate and normal LV function.

METHODS

Subjects: Patients who had documented CAD (n = 58) were enrolled; 20 patients had severe LV dysfunction (ejection fraction ≤30%), 16 had mild to moderate LV dysfunction (ejection fraction 30% to 50%), and 22 had normal LV function (ejection fraction ≥50%). Ejection fraction was determined by previous clinical catheterization in 34 patients and by gated single-photon emission computed tomography conducted in 24 patients at the time of study testing. In patients who had the 2 measurements, catheterization and gated single-photon emission computed tomographic ejection fraction measurements correlated (r = 0.75, p <0.001). The average time between previous angiography and testing for this study was 31.9

From the Saint Francis Hospital, Roslyn, State University of New York at Stony Brook, Stony Brook, New York; the Uniformed Services University of the Health Sciences, Bethesda, Maryland; Arrhythmia Associates and INOVA Fairfax Hospital, Fairfax, Virginia; the Veterans Affairs Medical Center, Washington, D.C.; the Cedars-Sinai Medical Center, Los Angeles, California; and the University of Maryland Hospital, Baltimore, Maryland. This study was supported in part by grant HL4733 from the National Institutes of Health, Bethesda, Maryland. Manuscript received September 8, 2004; revised manuscript received and accepted September 23, 2004.

Address for reprints: Olakunle O. Akinboboye, MD, Non-Invasive Laboratory, Saint Francis Hospital, 100 Port Washington Boulevard, Roslyn, New York 11576. E-mail: ooa2@columbia.edu.

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TABLE 1 Clinical and Demographic Characteristics of Left Ventricular (LV) Function Groups

Variable	LV Dysfunction		
	None (n = 22)	Mild to Moderate (n = 16)	Severe (n = 20)
Ejection fraction (%)	59.73 ± 5.82	38.50 ± 4.93*	25.10 ± 4.15*
Age (yrs)	62.82 ± 8.71	61.63 ± 7.99	59.65 ± 11.88
Women	2 (9%)	1 (6%)	3 (15%)
Whites	17 (77%)	15 (94%)	16 (80%)
African-Americans	3 (14%)	1 (6%)	3 (15%)
Implantable cardioverter-defibrillator	8 (36%)	14 (88%)*	19 (95%)*
Implantable cardioverter-defibrillator indications			
Sudden death	1 (13%)	1 (7%)	0 (0%)
Syncope with ventricular tachycardia/ventricular fibrillation	2 (25%)	7 (50%)	4 (21%)
Symptomatic ventricular tachycardia	2 (25%)	1 (7%)	7 (37%)
Other	3 (37%)	5 (36%)	8 (42%)
Previous coronary artery bypass grafting	10 (45%)	6 (38%)	12 (60%)
Previous myocardial infarction	10 (45%)	11 (69%)	18 (90%)
Hypertension	17 (77%)	13 (81%)	13 (65%)
β Blockers	14 (64%)	13 (81%)	15 (75%)
Calcium channel blockers	5 (23%)	0	4 (20%)
Nitrates (%)	3 (14%)	3 (19%)	4 (20%)
Angiotensin-converting enzyme inhibitors (%)	10 (45%)	9 (56%)	13 (65%)

*$p < 0.05$ versus normal LV function; †$p < 0.05$ versus mild to moderate LV dysfunction.

months, and no patient whose ejection fraction was determined at catheterization had an intervening myocardial infarction between angiography and the study.

Outpatients of participating hospitals who were 21 to 80 years old and had stable CAD that was confirmed by previous clinical coronary angiography and/or previous myocardial infarction were enrolled. Exclusion criteria were nonischemic cardiomyopathy, recent myocardial infarction (<1 month), recent percutaneous coronary angioplasty, planned coronary artery bypass surgery, severe congestive heart failure, stroke, atrial fibrillation, left bundle branch block, significant neurologic or psychiatric abnormality, unstable angina, and critical valvular pathology. Forty-one of 58 patients who were enrolled had implanted automatic cardioverters-defibrillators. There were more patients who had implanted automatic cardioverters-defibrillators in the 2 LV dysfunction groups than in the normal LV function group ($p < 0.05$). LV function groups did not differ in reasons for device implantation (Table 1).

When medically permissible, β blockers and long-acting nitrates were withheld ≥36 hours before testing in 11 patients and 1 patient, respectively.[5] Thirty-one patients were tested while on β-blocker therapy and 8 patients were tested while using long-acting nitrates. Calcium antagonists and angiotensin-converting enzyme inhibitors were withheld ≥20 hours before testing in 3 and 2 patients, respectively. Six patients were tested while on therapy with calcium antagonists and 30 patients were tested while on therapy with angiotensin-converting enzyme inhibitors.

Study procedures: The institutional review boards in the participating institutions approved the study, and written informed consent was obtained from all subjects. Patients were studied after an overnight fast. An intravenous line was inserted and ~3.5 mCi of thallium-201 was injected after subjects had rested for ≥15 minutes. Perfusion imaging at rest was started ~20 minutes after isotope injection. Subsequently, subjects underwent bicycle and mental stress testing with myocardial perfusion scintigraphy using technetium-99m sestamibi on consecutive days in random order.

Myocardial scintigraphy: Dual isotope single-photon emission computed tomography was used to assess myocardial ischemia induced by mental and physical stresses[16] because of its suitability in patients who have decreased LV function and in whom methods that require determination of further decreases in wall motion can be problematic.[16–18] Thallium-201 (2.5 to 3.5 mCi) was injected at rest and single-photon emission computed tomographic images were obtained 10 minutes after the injection. During mental stress, 20 to 30 mCi of technetium-99m sestamibi was injected.[22] Myocardial perfusion images were acquired with a dual-head single-photon emission computed tomographic camera (ADAC-Phillips, Milpitas, California) using circular 180° acquisitions of 64 projections at 20 seconds per projection for technetium-99m sestamibi and 32 projections at 40 seconds per projection for thallium-201 images. A 20% window centered on the 70-keV peak and a 10% window centered on the 167-keV peak of thallium-201 were used for acquisition of scans at rest. A 15% window centered on the140-keV peak of technetium-99m was used for acquisition of scans after stress. Images were acquired on a 64 × 64 matrix, and preprocessing was performed with a Butterworth filter with an order of 5 and cut-off frequency of 40% Nyquist for thallium-201 images and an order of 2.5 and cut-off frequency at 60% Nyquist for technetium-99m sestamibi. After back-projection with a ramp filter, images were reconstructed into transaxial tomograms and reoriented into short-axis, horizontal long-axis, and vertical long-axis images.

Mental stress test: Subjects were connected to an electrocardiograph and blood pressure monitor. Heart

rate, blood pressure, and 12-lead electrocardiogram were obtained at baseline and every 90 seconds during mental stress. Subjects were asked to recall a recent anger-provoking incident and discuss the circumstances of the incident in front of members of the research team.[19] Subsequently, a 4-minute math task was administered. Patients were asked to subtract 7 serially from 1,000 as rapidly and accurately as possible for 5 minutes and urged frequently to go faster and be more accurate. Approximately 30 mCi of technetium-99m setamibi was injected at 2 minutes into the first task; injection was delayed until 110% of baseline heart rate was achieved if this value was not reached at 2 minutes. Approximately 1 hour after isotope injection, subjects underwent single-photon emission computed tomographic myocardial imaging.

Bicycle stress test: Heart rate, blood pressure, and a 12-lead electrocardiogram were recorded at baseline and every 2 minutes during bicycle stress testing. Subjects were required to pedal the bike to match the beat of a metronome. Exercise was terminated if the patient developed moderate chest pain, shortness of breath, >2 mm horizontal or downsloping ST-segment depression, severe ventricular arrhythmias, hypotension, excessive fatigue, or if 85% maximum heart rate was reached and maintained. Resistance on the pedals was increased by 25 W every 3 minutes from 25 W at onset of exercise until a patient attained maximal effort tolerance, after which pedal resistance was held constant and approximately 30 mCi of technetium-99m sestamibi was injected. Patients exercised for 2 minutes after isotope injection. Myocardial perfusion imaging was commenced ~1 hour after isotope injection.

Image analysis: At a central core laboratory (Cedars-Sinai Medical Center, Los Angeles, California), a trained technologist who was blinded to clinical information and type of stress testing processed the images. Image analysis was performed with Quantitative Perfusion Scoring software (Cedars-Sinai Medical Center) using a 20-segment, 5-point scoring model (0 = normal, 1 = mildly decreased uptake, 2 = moderately decreased uptake, 3 = severely decreased uptake, and 4 = no uptake). Summed scores at rest and during stress were calculated from corresponding scans. Summed difference scores between scores during stress and at rest were used to determine stress-induced ischemia as absent (0 to 3) or present (>3).[20–22]

Statistical analysis: Results are expressed as mean ± SD or as percentages where appropriate. Changes in hemodynamic indexes were calculated as rest to peak exercise and rest to mean mental stress responses. Differences between groups were assessed by Student's *t* test, analysis of variance with Tukey's post hoc tests for continuous variables, and chi-square analysis for categorical variables, and log-linear analysis was conducted to assess whether the difference in prevalence between ischemia induced by mental stress and that induced by exercise differed across LV function groups. Logistic regression analysis was used to determine whether LV function status accounted for differences in ischemia after adjustments for other potential confounding or risk factor variables. A summed risk index was computed from the dichotomous variables of smoking status (previous, current, or never), history of hypercholesterolemia (yes or no), history of diabetes (yes or no), and history of hypertension (yes or no) to include in the logistic regression analyses. A 2-tailed p value <0.05 was adopted in analyses, unless otherwise noted.

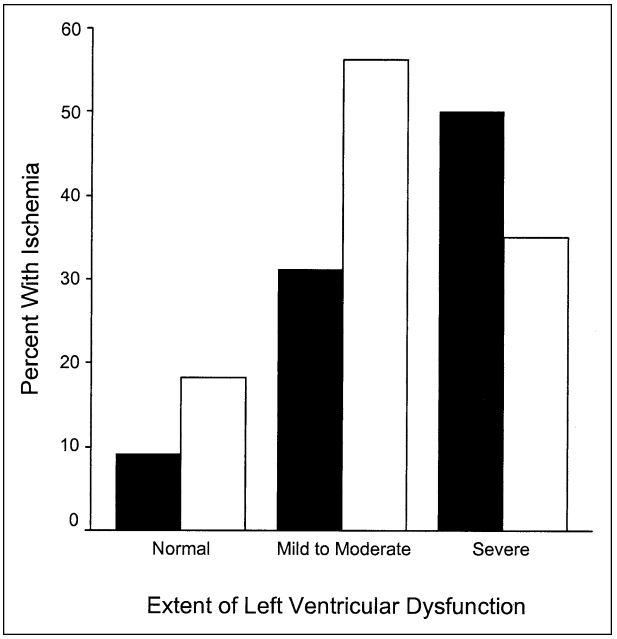

FIGURE 1. Percentages of patients who had ischemia induced by mental stress *(black columns)* and by exercise *(white bars)* by LV function group.

RESULTS

Clinical and demographic characteristics: Frequency of anginal complaints and extent of angiographic disease assessed visually were not different across the 3 groups.

Mental stress ischemia: Ischemia during mental stress (summed difference score >3) occurred in 17 of 58 patients (29%). It was induced more frequently in the severe LV dysfunction group (10 of 20, 50%) than in the normal LV function group (2 of 22, 9%; odds ratio [OR] 10, p <0.01). Ischemia induction with mental stress in the mild to moderate LV dysfunction group was intermediate in frequency (5 of 16, 31%) but did not significantly differ from the normal LV function group (OR 4.5, p = 0.10) or the severe LV dysfunction group (OR 2.2, p = 0.26) (Figure 1).

Comparisons between exercise and mental stress: Of 58 patients, 12 had ischemia induced by mental stress and exercise, 8 had ischemia with exercise only, 5 had ischemia with mental stress only, and 33 did not have ischemia with either stressor. Ischemia with exercise occurred in 20 of 58 patients (35%; Figure 1). Ischemia was induced more frequently with exercise in the mild to moderate LV dysfunction group (9 of 16, 56%) than in the normal LV function group (4 of 22,

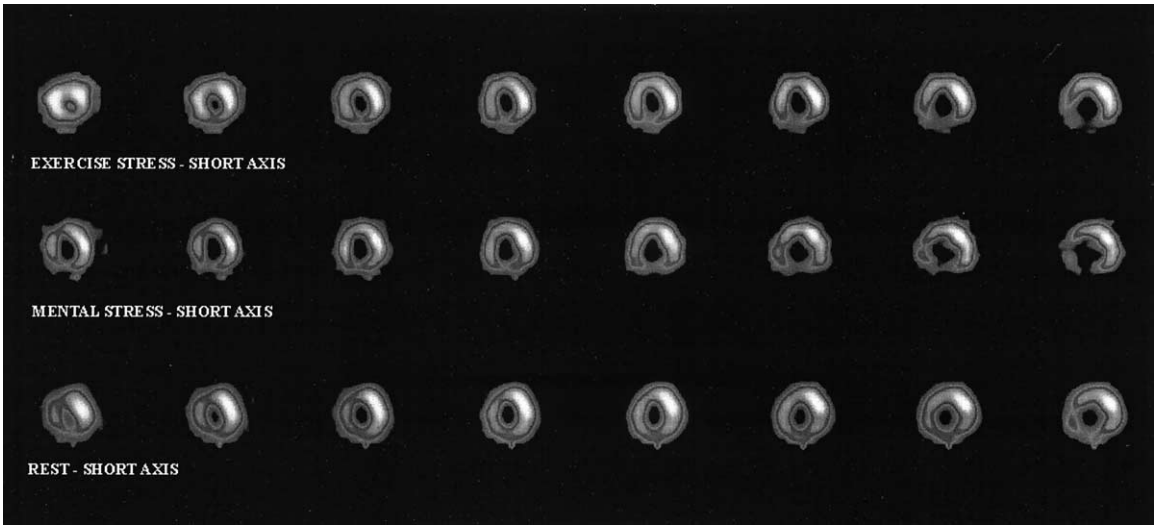

FIGURE 2. Short-axis tomograms display large and severe inferior and basal septal perfusion defects recorded during exercise testing and mental stress, with partial reversibility on the scan taken at rest. The magnitude and severity of the count decrease are similar on the 2 scans taken during stress.

18%; OR 5.8, p = 0.019). However, the frequency of ischemia with exercise in the severe LV dysfunction group (7 of 20, 35%) did not differ from that in the normal LV function group (18%; OR 2.4, p = 0.22) or mild to moderate LV dysfunction group (56%; OR 2.4, p = 0.21) (Figure 1).

LV ejection fraction was significantly lower in patients who had ischemia induced by mental stress than in those who did not (33 ± 12% vs 46 ± 16%, respectively, p = 0.004). However, there was no significant difference in LV ejection fraction at rest between patients with exercise-induced ischemia and those without (38 ± 14% vs 44 ± 17% respectively, p = 0.13).

Among those patients who had ischemia, severity of ischemia (summed difference score) was comparable for mental stress (5.75 ± 1.48) and exercise (6.5 ± 2.2; p = 0.24; Figure 2).

Logistic regression analyses were adjusted for age, summed risk index, number of diseased vessels, and number of previous myocardial infarctions. After controlling for these variables, LV function type accounted for a substantial proportion of the variance in ischemia induced by mental stress (p = 0.07). Multivariate analysis associated severe LV dysfunction with a higher frequency of ischemia induced by mental stress compared with normal LV function (OR 12.4, p = 0.021). Similarly, the LV function group was significantly associated with exercise-induced ischemia (p = 0.007), with contrasts indicating significantly more exercise-induced ischemia in the mild/moderate LV dysfunction group versus the normal LV function group (OR 22.05, p = 0.002).

We next compared frequency of ischemia induced by mental stress versus that induced by exercise for the 3 LV function groups (Figure 1) using log-linear analysis. There was a difference in the frequency of ischemia induced by mental stress versus that induced by exercise in the severe LV dysfunction group (p = 0.06) and mild to moderate LV dysfunction group (p = 0.07) but not in the normal LV function group (p = 0.31); however, the pattern of ischemia induced by mental stress versus that induced by exercise differed between groups (p <0.02). For the mild to moderate LV dysfunction group, there was more ischemia induced by exercise than by mental stress, whereas the severe LV dysfunction group had more ischemia induced by mental stress than by exercise. Further analysis showed that the prevalence of ischemia induced by mental stress versus that induced by exercise was significantly different for the severe LV dysfunction group compared with the mild to moderate LV dysfunction group (p = 0.013) and normal LV function group (p = 0.044). This result indicated that the severe LV dysfunction group had a higher prevalence of ischemia induced by mental stress than by exercise, with no such difference among patients who had normal LV function and the opposite result for patients who had mild to moderate LV dysfunction.

Hemodynamics: exercise versus mental stress and effects of LV dysfunction: Comparable numbers of patients in each group reached age-predicted target heart rates during exercise, although exercise time was decreased in the severe LV dysfunction group. Mental stress and exercise produced significant increases in systolic blood pressure, diastolic blood pressure, heart rate, and double product (p <0.001), with all groups increasing from rest to stress for all hemodynamic measurements during mental and exercise stress. Average heart rate increased by 11 beats/min, whereas systolic and diastolic blood pressures and double product increased by 30 ± 19 mm Hg, 17 ± 11 mm Hg, and 3,206 ± 1,740 beats/min-mm Hg, respectively, during mental stress. Exercise increased heart rate by 51 ± 20 beats/min, systolic blood pressure by 34 ± 22 mm Hg, diastolic blood pressure by 9 ± 14 mm Hg, and double product by 10,472 ± 4,157 beats/min-mm Hg. Values in each group increased similarly

from rest to stress (mental and exercise stresses) for all hemodynamic measurements, except heart rate with mental stress, for which values within the severe LV dysfunction group increased more than those within the normal LV function group ($p = 0.01$).

DISCUSSION

Our results demonstrated that, at roughly comparable double products, patients who have severe LV dysfunction are more susceptible to ischemia with mental stress than are patients who have normal LV function. Moderate LV dysfunction is associated with an intermediate frequency of ischemia induced by mental stress. These differences in ischemia induced by mental stress remained after adjusting for potential confounders, including number of narrowed/diseased coronary arteries, number of previous myocardial infarcts, and presence of risk factors. In addition, perfusion defects demonstrated with mental stress occurred with similar or lower frequency than did exercise-induced ischemia in patients who had normal LV function or moderate LV dysfunction. Among patients who had severe LV dysfunction in this sample, the frequency of ischemia induced by mental stress was higher than that induced by exercise.

The difference in frequency of ischemia induced by mental stress between patients who had severe LV dysfunction and those who had normal LV function might be attributable to the mechanisms of ischemia induced by mental stress in conjunction with preexisting pathophysiologic processes that are evident with LV dysfunction. In addition to causing a modest increase in LV oxygen demand, mental stress can induce coronary vasoconstriction due to sympathetic activation.[4,5,14,20–24] Increased coronary resistance secondary to coronary vasoconstriction would result in a greater decrease in myocardial perfusion in dysfunctional versus normal myocardium because, in general, LV end-diastolic pressure is higher in patients who have LV dysfunction. Coronary vasoconstriction and increased LV end-diastolic pressure could decrease the effective perfusion pressure gradient across the coronary vascular bed, thus causing perfusion abnormalities.

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